Assessing Neurosensory Consequences of Energy Directed to the Head

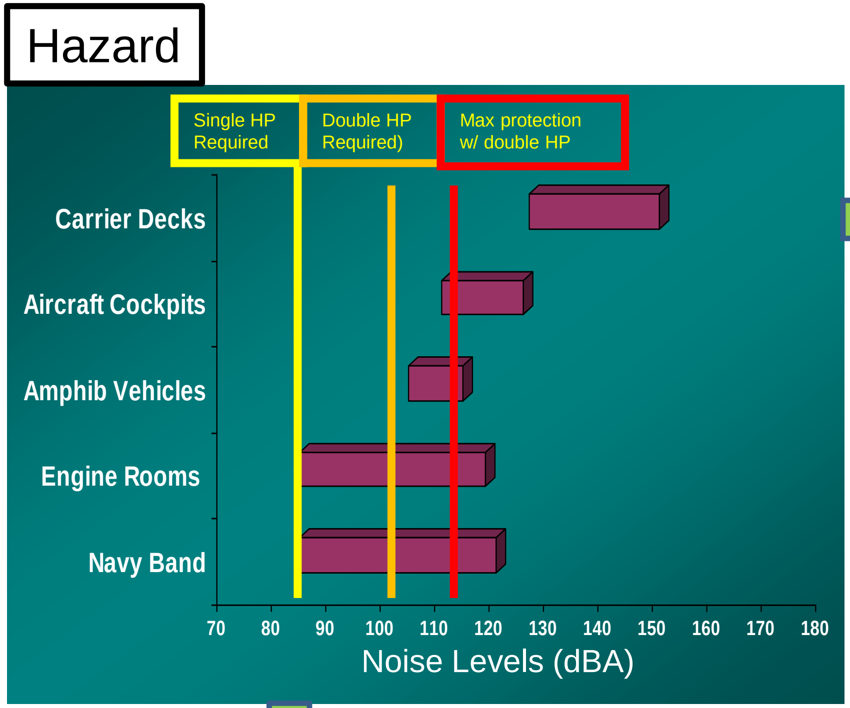
Carey D. Balaban

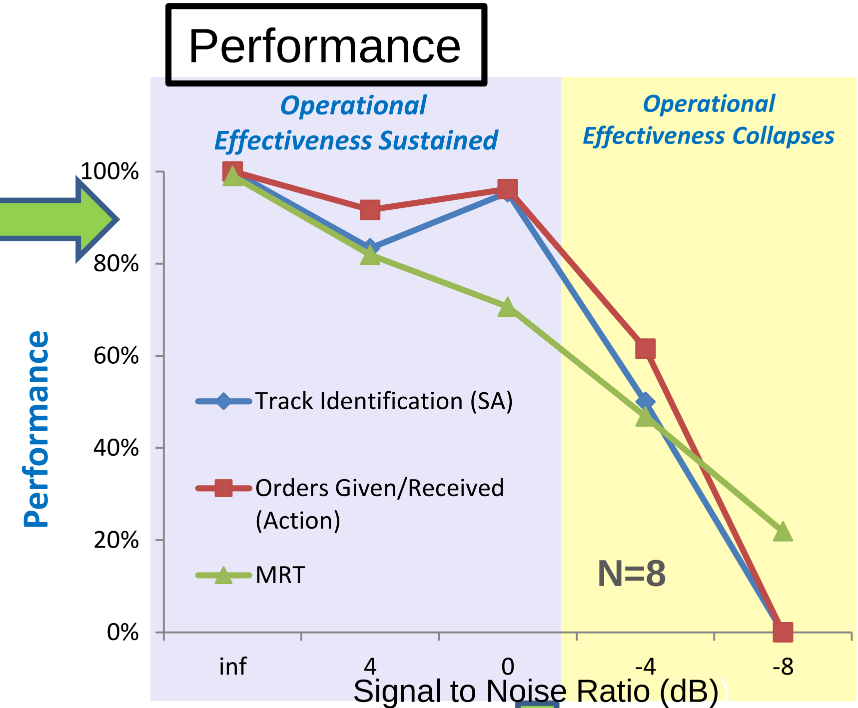
University of Pittsburgh

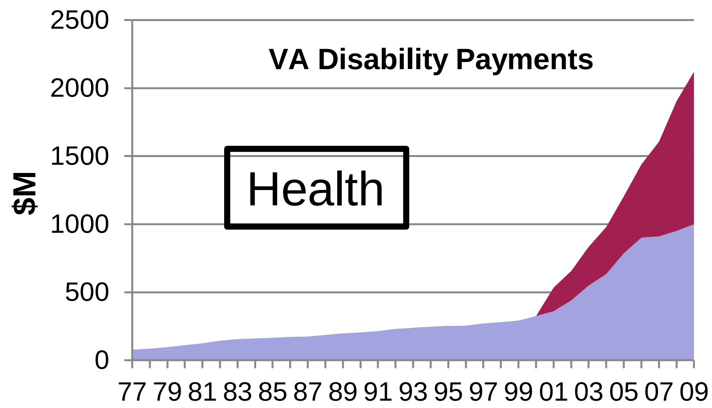
(ONR NIHL Program Component)

Noise-Induced Hearing Loss

Warfighter Performance S&T







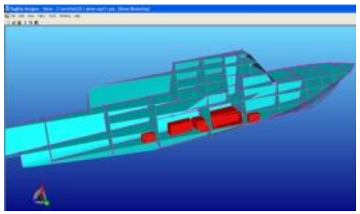
Hazardous Noise Impacts Performance/Health

Noise-Induced Hearing Loss Portfolio

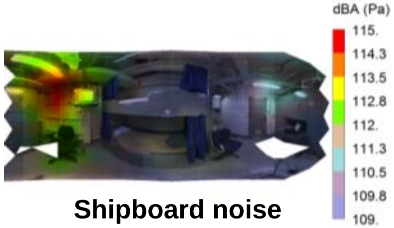
Warfighter Performance S&T

Systems Approach for an Integrated 6.1 / 6.2 / 6.3 Program

Source Noise Reduction

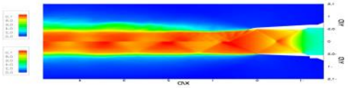


Shipboard noise assessment



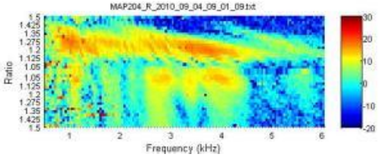
Shipboard noise path validation

Jet noise Reduction



Laboratory modeling/ scale tests of jet noise reduction

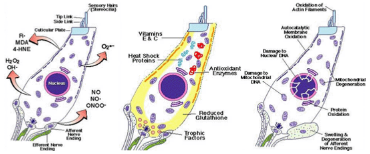
Incidence, Susceptibility & Evaluation



Assessment tools

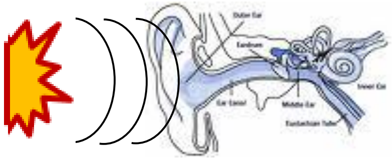
Hearing loss simulator

Medical Prevention & Treatment

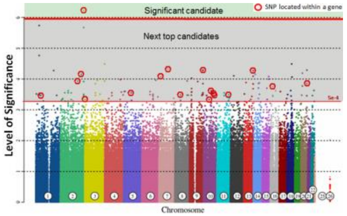


Cell regeneration

Pharmacologic interventions and drug delivery



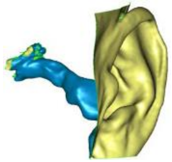
Blast Auditory Injuries



NIHL markers

Personal Protective Equipment (PPE)

Shipboard PPE



3D Digitization for "Prescription" Ear Plugs

In-Ear Dosimetry

Underwater comms & hearing protection

Development Through NIHL

OPEN ACCESS Freely available online PLOS | ONE

Amelioration of Acute Sequelae of Blast Induced Mild Traumatic Brain Injury by N-Acetyl Cysteine: A Double-Blind, Placebo Controlled Study

Michael E. Hoffer[1*¶], Carey Balaban[2¶], Martin D. Slade[3], Jack W. Tsao[4], Barry Hoffer[5]

- NAC developed originally as protective agent (anti-oxidant and anti-inflammatory) against NIHL in animal models
- NAC does not cross intact blood-brain-barrier, but crosses injured barrier

Development Through NIHL

- **NAC efficacious in theater against mild blast-related TBI**
  - **Subject to clinical trials by others**
- **Need for better assessment of mild TBI has fostered development of goggle technologies for assessing eye movements**

mTBI is a Directed Energy Effect

- **Vestibular, oculomotor and reaction time tests provide objective metrics for acute mTBI**

Prospects for Operational Monitoring of Eye and Pupil Movements

- Coordinated movements of the eyes in the orbit, lens (accommodation) and pupil are used to acquire and analyze visual information
  - Effectors are extraocular muscles, ciliary muscle and iris dilator and sphincter muscles
- Eye movements may be conjugate (both eyes move in parallel with the same magnitude and direction) or disconjugate

Prospects for Operational Monitoring of Eye and Pupil Movements

- Conjugate movements (symmetric):
  - Saccadic eye movements: ballistic orientation of fovea to new target, followed by fixation (dwell)
  - Smooth pursuit: maintain foveal fixation on slowly moving target (tracking)
  - Nystagmus: alternating fast (refixation) and slow (tracking) phase movements
    - Vestibular: slow phase compensates for head movement
    - Optokinetic: slow phase tracks peripheral optic flow

Prospects for Operational Monitoring of Eye and Pupil Movements

- Disconjugate Eye Movements (convergence and divergence)
  - Near response during convergence: Eyes converge, lens curvature increases, and pupil constricts (e.g., focus on near or approaching target)
  - Near response during divergence: Eyes diverge, lens curvature decreases, and pupil dilates (e.g., focus on far or receding target)

Prospects for Operational Monitoring of Eye and Pupil Movements

- Video-oculography permits unobtrusive monitoring of eye and pupil movements.
- Eye is imaged with digital video with infrared diode illumination
- Pupil detected and measured
- Rotation of eyeball calculated with algorithms from center of mass of pupil and iris features

Neurologic Assessment with Video-Oculography

- Eye movement motor performance dynamics (current clinical applications)
- Eye movements as components of cognitive tasks
  - Predictive saccades
  - Anti-saccade task
  - Reaction time paradigms
    - Single task
    - Dual/multitask interference
  - Gaze dwell times

Vestibular, Oculomotor and Reaction Time Assessment in the Laboratory or Office

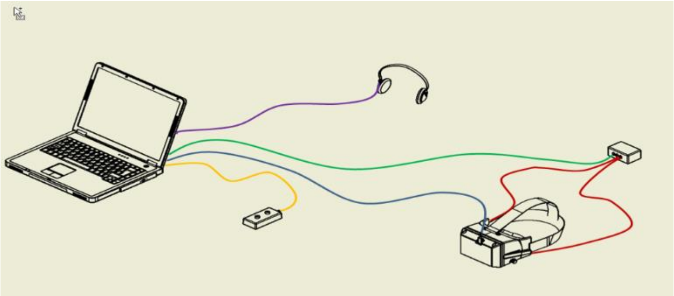
I-Portal® NOTC (Neuro-Otologic Test Center)

I-Portal ® PAS (Portable Assessment System-integrated head-mounted display and eye-tracking)

- **Purpose:**
  - Assess neuro-sensory integrity,
  - By measuring the performance of functional systems that span a broad range of neuro-sensory anatomy.
- **Oculomotor, Vestibular and Reaction Time Measures :**
  - Oculomotor Responses
  - Vestibular Performance
  - Reaction Time (Auditory, Visual and Combination- visual reaction time and oculomotor)

Hardware and Software

- Conducted with the I-PAS™ (I-Portal® Portable Assessment System, NKI Pittsburgh), a portable 3D head mounted display (HMD) system with integrated eye tracking technology.
  - Sampling rate 100 Hz
  - Resolution < 0.1°
- All stimuli are created in a virtual environment.
- Neuro Kinetics VEST™ software was used to run the battery of tests and analyze the data.



Operational Scenario for Technology

AP

US makes Cuba embassy cuts permanent after ‘health attacks’

By JOSH LEDERMAN and MATTHEW LEE
Mar. 02, 2018

https://apn

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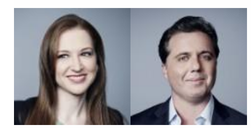
WASHINGTON (AP) — Citing mysterious “health attacks” in Havana, the United States said Friday it is making permanent its withdrawal of 60 percent of its diplomats from Cuba, extending an action that has hurt the island nation’s economy and cramped Cubans’ ability to visit the U.S.

Last October, the State Department ordered non-essential embassy personnel and the families of all staff to leave Havana,

US Embassy in Cuba to reduce staff indefinitely after 'health attacks'



By Laura Koran and Patrick Oppmann, CNN
Updated 6:38 PM ET, Fri March 2, 2018

The American flag flies at the U.S. Embassy following a ceremony August 14, 2015, in Havana.

Colleagues

- Carey D. Balaban (University of Pittsburgh)
- Michael E. Hoffer (University of Miami)
- Bonnie Levin (University of Miami)

Assessing Effects in Havana

- **Late 2016 – 2017, reports of sudden onset dizziness, ear pain and tinnitus in diplomats and family members (no DoD personnel)**
- **Many reported hearing a loud, high frequency, very localized sound capable of following them in a room**
- **Some reported a pressure sensations localized in a room**

Assessing Effects in Havana

- Over 140 individuals with suspected exposures were examined at University of Miami or in Havana, Cuba
- Identified 35 individuals with appropriate history, symptoms and perceived exposure
  - Perception of sound or pressure
  - In same room with a person with perception

Assessing Effects in Havana

- The 35 individuals examined at University of Miami, Miller School of Medicine, 7-60 days after most recent reported exposure
- 21 males, 14 females; 42.3 ± 11.3 years, all <64 years old
- Comprehensive history, physical exam which include, standard eye movement testing
- Specialized clinical and neuropsychological testing based on history and physical exam
  - Subsets received specialized testing needed to confirm a diagnosis

Assessing Effects in Havana

- Exams of ten individuals with no symptoms were within normal limits (Unaffected Group)
  - One reported a ‘force wave’ sensation
  - One reported a single but very brief perception of high pitched sound
  - Eight were present in the same room as someone reporting an exposure

Symptom Reports

SYMPTOM	Unaffected group	Affected Group
Dizziness (Yes:No)	0:10 (0%)	23:2 (92%)*
Cognitive (Yes:No)	0:10 (0%)	14:11 (56%)*
Hearing Loss (Yes:No)	0:10 (0%)	8:17 (32%)*
Tinnitus (Yes:No)	0:10 (0%)	8:17 (32%)*
Ear Pain (Yes:No)	0:10 (0%)	7:18 (28%)*
Headache (Yes:No)	2:8 (25%)	6:19 (24%)
MULTIPLE SYMPTOMS		
At least 2 Symptoms (including HA/excluding HA, Yes:No)	0:10/0:10	24: 1/24:1**
At least 3 Symptoms (including HA/excluding HA, Yes:No)	0:10/0:10	16:9 /14:11**

*Significant difference compared to asymptomatic group, Fisher exact test, $p<0.01$

**Both values are significantly different compared to the asymptomatic group, Fisher exact test, $p<0.01$

Clinical Findings

CLINICAL FINDING (Affected Patients)	Number Tested	Abnormal	Within Normal Limits
Subjective Visual Vertical (SVV)	25	23	2
Chair Rotation HVOR	11	9	2
Central Vestibular Findings		6	5
Antisaccade test (abnormal error rate)	23	12	11
Cervical Vestibular Evoked Myogenic Potential (cVEMP)	9	7	2
Ocular VEMP (oVEMP)	9	7	2

Cognitive and Neuropsychologic Findings

Case #	Premorbid estimate of intellect	Subjective complaints	Neuropsychological Findings
1	NART=114; High Average	• Forgetfulness • Mental fog/Slow performance • Difficulty with complex attention • Reduced motivation	• Diminished working memory • Slowed processing speed • Inefficient verbal learning • Reduced verbal fluency • Weak grip strength
2	NART=114; High Average	• Forgetfulness • Poor concentration/planning difficulty • Difficulty retrieving words • Mood swings • Increased irritability • Lack of motivation	• Mildly impaired verbal learning and memory • Mild attentional problems • Reduced word finding • Mild depression
3	NART=117; High Average	• Slower processing • Difficulty multi-tasking • Difficulty retrieving words • Greater level of effort required to complete simple tasks	• Reduced speed of processing Weak grip strength • Diminished sustained attention/ problems sustaining mental set • Difficulty making rapid visual comparisons

Abbreviation: NART- National Adult Reading Test

Cognitive and Neuropsychologic Findings

Case #	Premorbid estimate of intellect	Subjective complaints	Neuropsychological Findings
4	Average	• Slower processing • Attentional problems	• Slow processing speed
5	NART=117; High Average	• Slower processing • Difficulty concentrating • Difficulty multitasking • Feeling confused • Irritability	• Reduced ability to focus in the face of competing stimuli • Episodic memory • Attention • Working memory difficulties • Weak grip strength.
6	NART=106; Average	• Forgetfulness • Slower processing • Poor concentration • Word finding difficulties • Indecisiveness • Irritability, increased tearfulness • decreased interest in activities, anxiety & mood swings	• Difficulty with verbal memory • Reduced fine motor speed • Reduced ability to focus in the face of competing stimuli • Poor Grip Strength • Moderate depression • Mild Anxiety and apathy

Cognitive and Neuropsychologic Findings

Case #	Premorbid estimate of intellect	Subjective complaints	Neuropsychological Findings
7	NART=115; High Average	• Forgetfulness • Slower processing • Difficulty retrieving words • Mood lability & anxiety	• Decreased visual memory • Reduced verbal fluency • Weak Grip Strength
8	NART=88; Low Average	• Forgetfulness • Slower processing • Poor concentration • Difficulties with organization • Difficulty monitoring • Word finding difficulties	• Difficulty with simple verbal and visual attention, visual processing • Reduced ability to focus in the face of competing stimuli • Reduced vocabulary • Mild depression
9	Average	• Poor concentration	• Slow processing speed • Diminished abstract problem solving

Summary

- **Extremely high incidence of objective signs (e.g., abnormal SVV, rotational testing and VEMPs) of underlying asymmetric vestibulopathies and otolithic abnormalities.**
- **Presentation more homogenous than most mTBI populations.**
- **Lower prevalence of headache than typical for mTBI.**

Summary

- Cognitive symptoms (e.g., problems maintaining sustained attention, slower processing speed, difficulty multi-tasking, and word retrieval difficulties) similar to mTBI or decompression sickness but more pervasive and consistently paired with emotional symptoms that included irritability, anxiety and depression.
- Elevated prevalence of abnormal anti-saccade task error rates.

Source of Exposure Unknown

- Potential directed energy sources include
  - Hypersonic sound
  - Pulsed radiofrequency
  - Pulsed laser source
  - Ultrasound (e.g., from photoacoustic device)
- Receiver characteristics: Waveguide, resonance and cavitation properties of intracranial contents

Caution re: Symptom Reports

- Causal attributions for symptoms associated with balance disorders and mTBI, including neuropsychological complaints, are unreliable.
  - Attribution obvious for overt exposure scenarios (blast wave exposure or blunt impact to the head)
  - Problematic for dizziness due to a covert cause. For example, ear pain and cognitive symptoms are aversive so may produce conditioned aversion with misattribution.
    - Analogy to conditioned taste aversion: nausea and the symptoms may be attributed to irrelevant but novel conditions that merely coincide temporally with the proximate cause.

Objective Assessment of Acute mTBI

PLOS | ONE

RESEARCH ARTICLE

Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury

Carey Balaban[1☯], Michael E. Hoffer[2,3,4☯*], Mikhaylo Szczupak[2,4], Hillary Snapp[2], James Crawford[5], Sara Murphy[2,6], Kathryn Marshall[5], Constanza Pelusso[2,4], Sean Knowles[2], Alex Kiderman[7]

Study Populations

- Number of mTBI subjects: **100 (two successive cohorts of 50)**
- Number of Control subjects: **200 (two successive cohorts of 100)**
- Number of Testing sites: **2 (**Naval Medical Center - San Diego & Madigan Army Medical Center)

Table 1. Tests performed.

Test	Variables
Optokinetic	Left and Right Gain and Asymmetry for nystagmus beats
Smooth Pursuit–Horizontal/Vertical	Percent of Saccadic Intrusions, Initiation Time
Saccade-Random–Horizontal/Vertical	Saccade Onset Latency, Accuracy, Peak Velocity
Predictive Saccade	Point in cycle at which subject anticipates/predicts the fixed timing interval and dot position as well as percent of correct predictions
Anti-saccade Horizontal	Number of Pro-saccadic errors, correct anti-saccades, Latency, and Velocity
Self-paced Saccade	Saccades per second
Gaze Horizontal	Vertical peak and average slow phase velocity
Visual Reaction Time	Mean and Standard Deviation (SD) of Latency
Auditory Reaction Time	Mean and SD of Latency
Saccade and Reaction Time	Saccade Onset Latency, Accuracy, and Latency and SD for motor responses
Computer Controlled Rotation Head Impulse Test (crHIT)	Left and Right Gain and Asymetey
Sinusoidal Harmonic Acceleration (SHA)	Gain, Phase, and Asymmetry—High Frequencies
Visual Enhancement	Gain, Phase, and Asymmetry—High Frequencies
Visual Suppression	Gain, Phase, and Asymmetry—High Frequencies

doi:10.1371/journal.pone.0162168.t001

Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

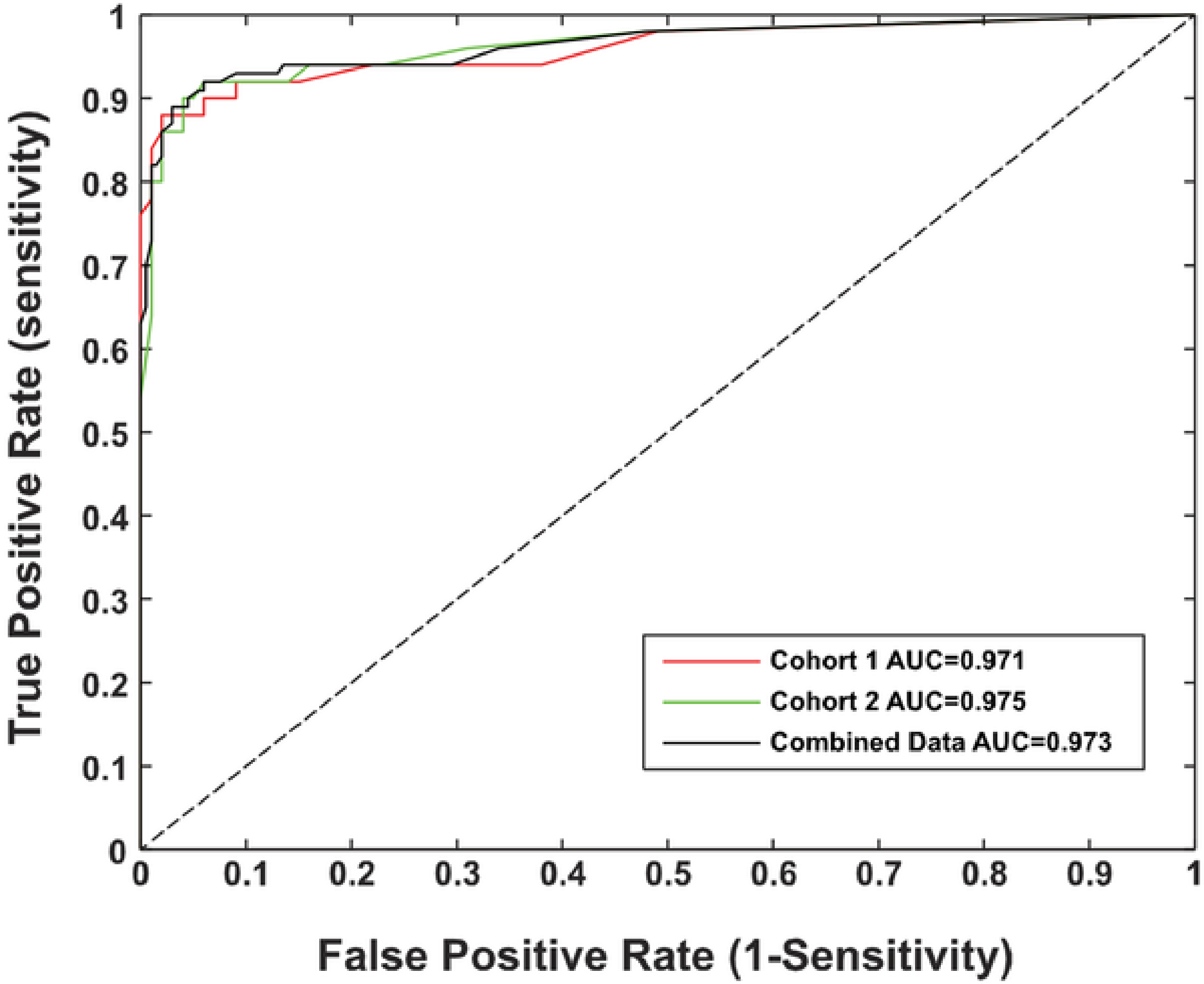
Table 2. Characteristics of the subject population.

	Control Group		mTBI Group	
	Cohort 1	Cohort 2	Cohort1	Cohort 2
Gender (Females: Males)	25:75	19:81	21:29	12:38
Sample size (N)	100	100	50	50
Age (years, mean ± SD)	29.7±6.2	26.3±6.0	26.7±6.4	26.0±7.0
Symptom Score (22 item SCAT, 22 minus number symptoms, mean ± SD)	20.2±2.7	20.6±2.4	8.5±6.3	8.3±6.0
Symptom Severity (22 item SCAT, mean ± SD, max 132)	2.9±5.1	2.4±5.4	44.5±26.8	43.2±30.5
Time post-TBI (hours, mean ± SD)			58.1±35.6	66.6±39.6
Glasgow Coma Scale (mean ± SD)			15.0±0.0	14.8±1.0
Functional Gait Index (maximum 30, mean ± SD)			24.7±4.6	25.7±5.8
Dizziness Handicap Inventory Total Score (mean ± SD)			33.5±24.1	28.5±20.0
Trail Making Test A (sec, mean ± SD)			29.1±11.5	31.1±12.1
Trail Making Test B (sec, mean ± SD)			55.4±18.5	56.9±28.9

doi:10.1371/journal.pone.0162168.t002

Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

Fig 1. ROC curve for Individual Cohorts and Combined Group.



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http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

Table 3. Parameters for logistic regression models and significance levels.

	Cohort 1		Cohort 2		Combined	
Parameter (coefficient)	Estimate ± SE	Wald	Estimate ± SE	Wald	Estimate ± SE	Wald
Prosaccade error (%)	0.129±0.034	13.97***	0.107±0.028	14.91***	0.117±0.021	31.00***
crHIT absolute gain symmetry	0.824±0.231	12.79***	1.099±0.280	15.43***	0.9297±0.166	31.32***
crHIT average gain	-32.216±8.901	13.10***	-36.603±10.039	13.29***	-32.058±6.025	28.30***
Predictive Saccades (number)	-0.190±0.077	6.18*	-0.204±0.071	8.26**	-0.195±0.050	15.51***
Intercept	26.212±8.024	10.67**	30.895±8.956	11.90***	26.456±5.461	23.47***

doi:10.1371/journal.pone.0162168.t003

Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

Table 4. Sensitivities and specificities.

	True Positive (Sensitivity)	True Negative (Specificity)	Correct	ROC AUC
Cohort 1: Data	88%	99%	95.3%	0.9714
Cohort 2: Data	92%	98%	96.0%	0.9752
Combined: Data	89.0%	97.5%	94.7%	0.9727
70/30 in-out sample	90.9%	98.5%	97%	0.9765
Leave one out	87%	97%	93.7%	

doi:10.1371/journal.pone.0162168.t004

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TENTH ANNIVERSARY

Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
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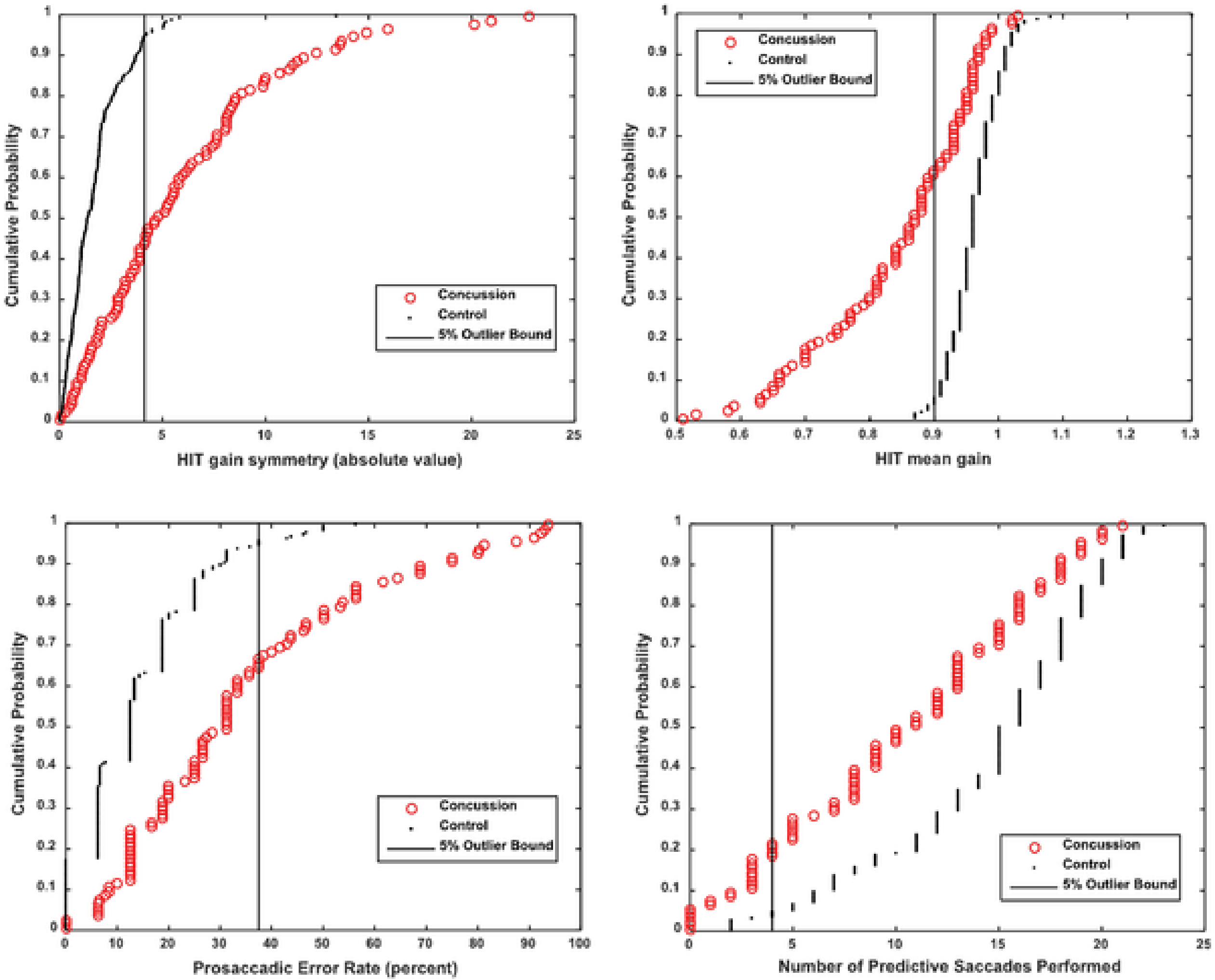
Fig 2. Cumulative distribution functions are shown for the four metrics in the logistic regression model, 89% sensitivity and 97.5% specificity.



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http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

Objective Assessment of Acute mTBI: Up to 2 Weeks Post-Injury

Laryngoscope Investigative Otolaryngology

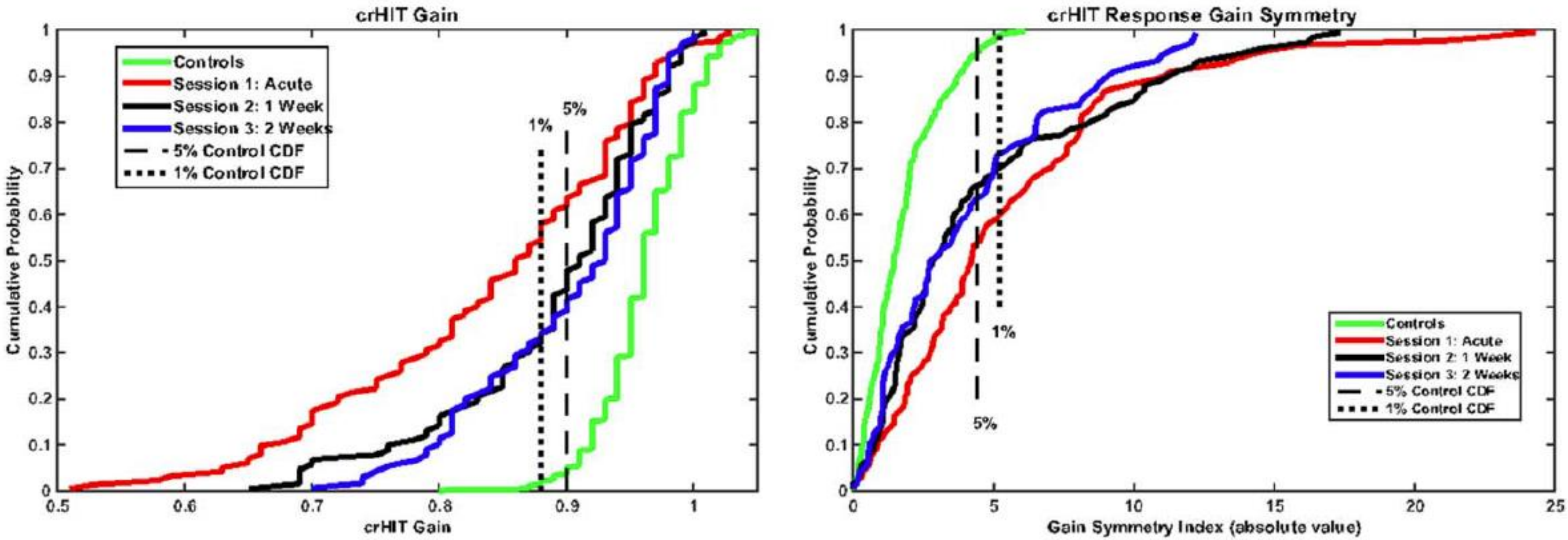
The Use of Oculomotor, Vestibular, and Reaction Time Tests to Assess Mild Traumatic Brain Injury (mTBI) Over Time

Michael E. Hoffer, MD *; Carey Balaban, PhD*; Mikhaylo Szczupak, MD; James Buskirk, PT; Hillary Snapp, AuD; James Crawford, MD; Sean Wise, MD; Sara Murphy, MPH; Kathryn Marshall, PhD; Constanza Pelusso, MD; Sean Knowles; Alex Kiderman, PhD

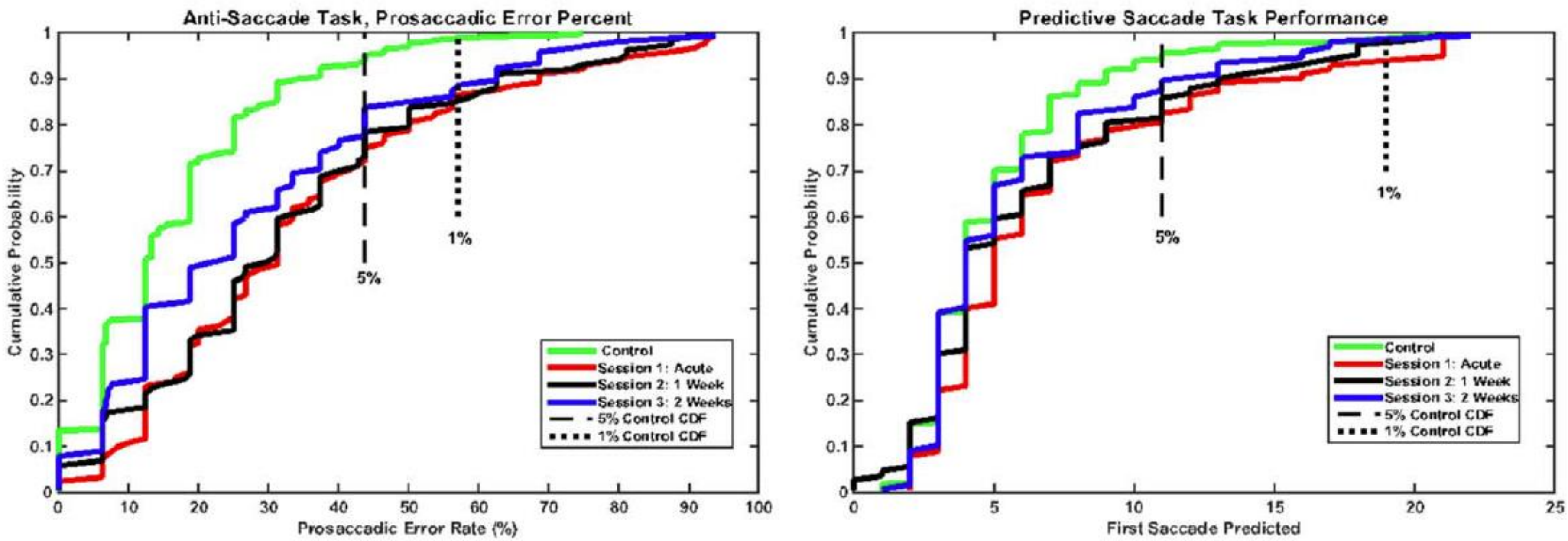
Subject Data

	Concussion Session 1		Concussion Session 2±		Concussion Session 3		No Concussion	
	Female (n=34)	Male (n=72)	Female (n=32)	Male (n=63)	Female (n=31)	Male (n=54)	Female (n=95)	Male (n=205)
Age	26.1 ± 6.1	26.2 ± 6.9					27.6 ± 6.9	27.3 ± 6.0
Symptom Severity Rating (SCAT2)	42.3 ± 24.9	42.5 ± 29.6	35.7 ± 26.9	29.5 ± 27.2	25.4 ± 25.7	23.9 ± 27.8	3.4 ± 6.5	2.6 ± 5.4
Time post-concussion (hr)	70.3 ± 44.3	59.3 ± 34.3	226.6 ± 72.3	213.9 ± 65.8	400.3 ± 78.6	398.3 ± 88.5		
FGA [≤22 fall risk]	25.1 ± 4.7 [5/34]	25.3 ± 4.6 [16/72]	26.5 ± 4.2 [2/32]	27.6 ± 3.3 [4/63]	28.1 ± 2.1 [1/31]	28.7 ± 2.1 [1/54]		
TMT A (sec)	32.4 ± 13.1	29.0 ± 10.7	22.7 ± 6.6	24.8 ± 13.3	20.1 ± 5.7	21.2 ± 12.4		
TMT B (sec) [norms: 49.8±12.5 sec]	52.5 ± 23.5	56.2 ± 23.7	45.1 ± 16.9	52.1 ± 22.9	37.9 12.9	43.1 ± 20.7		
DHI total [≥29 abnormal]	33.4 ± 22.3 [19/34]	30.4 ± 21.8 [30/72]	26.5 ± 23.0 [12/32]	22.1 ± 22.6 [21/63]	18.1 ± 21.9 [8/31]	17.6 ± 21.6 [13/54]		

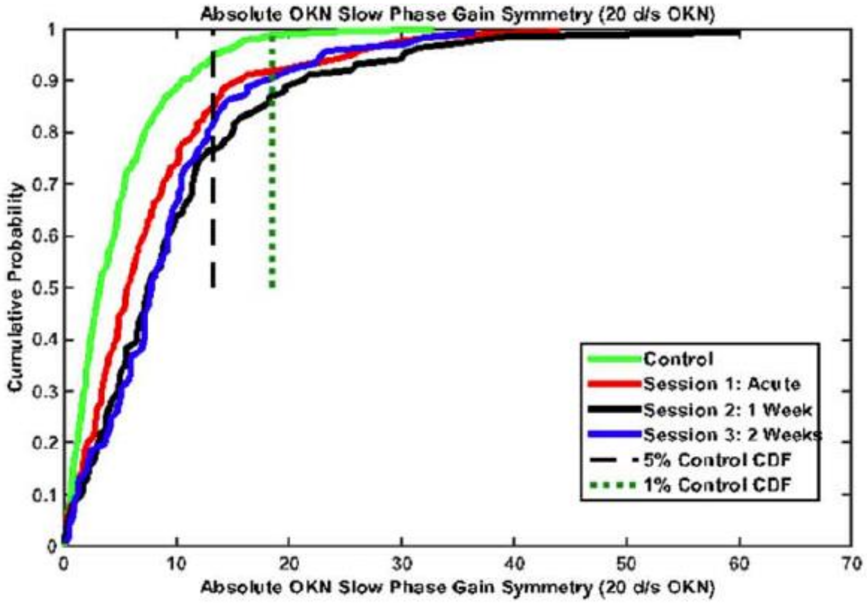
Key Measure Changes Across Sessions

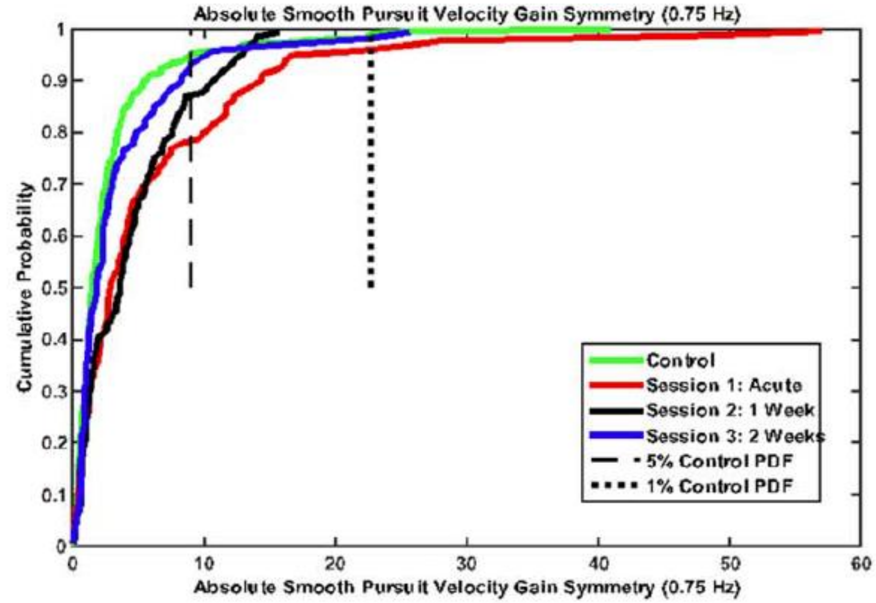


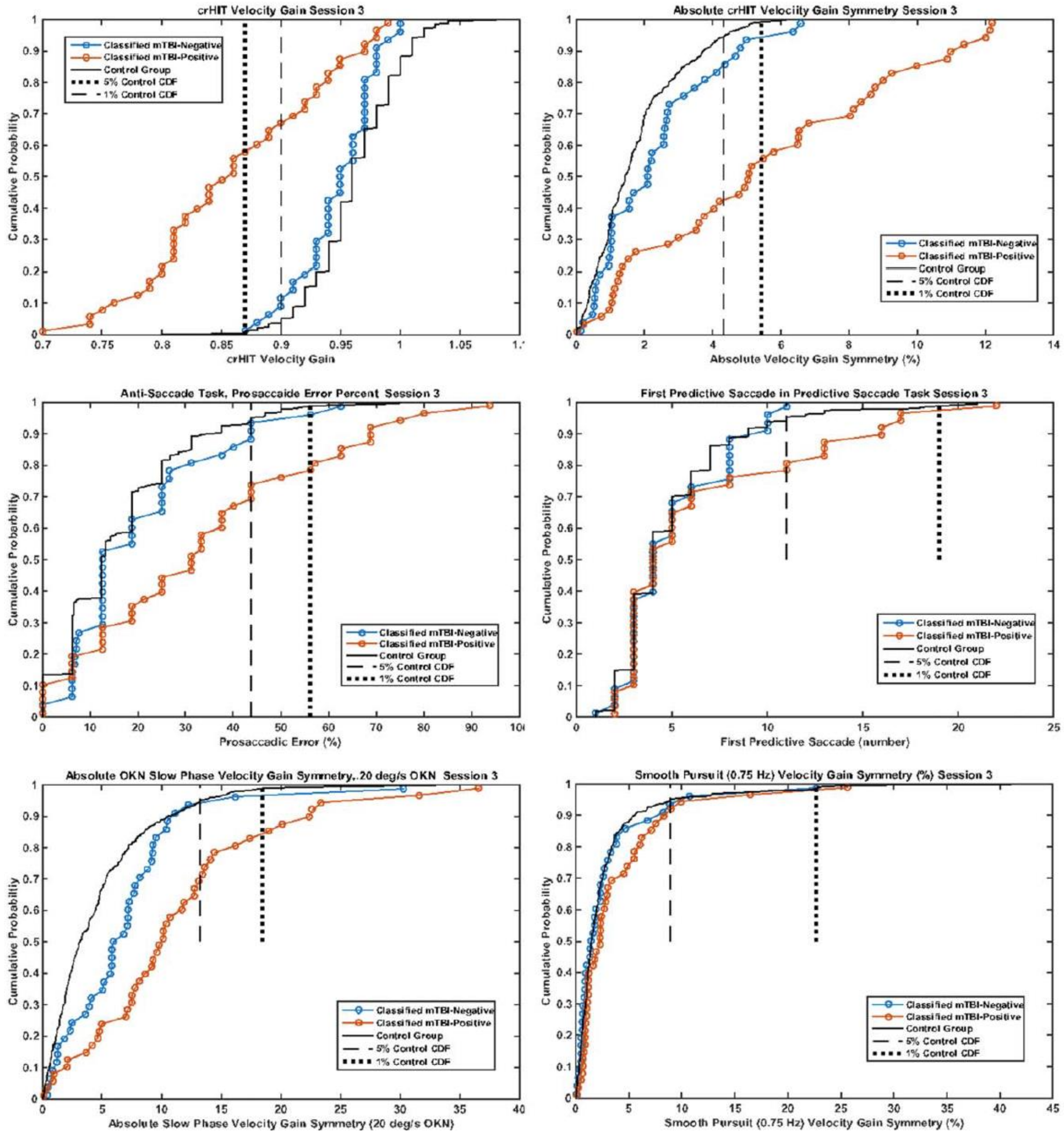
Key Measure Changes Across Sessions



Key Measure Changes Across Sessions







crHIT Velocity Gain Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
crHIT Velocity Gain
Absolute crHIT Velocity Gain Symmetry Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
Absolute Velocity Gain Symmetry (%)
Anti-Saccade Task, Prosaccaide Error Percent Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
Prosaccadic Error (%)
First Predictive Saccade in Predictive Saccade Task Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
First Predictive Saccade (number)
Absolute OKN Slow Phase Velocity Gain Symmetry,.20 deg/s OKN Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
Absolute Slow Phase Velocity Gain Symmetry (20 deg/s OKN)
Smooth Pursuit (0.75 Hz) Velocity Gain Symmetry (%) Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
Smooth Pursuit (0.75 Hz) Velocity Gain Symmetry (%)

Background

- Disconjugate eye movements (convergence and divergence) track objects that vary in depth over the binocular visual field. These eye movements can be measured objectively and are commonly affected following mTBI.

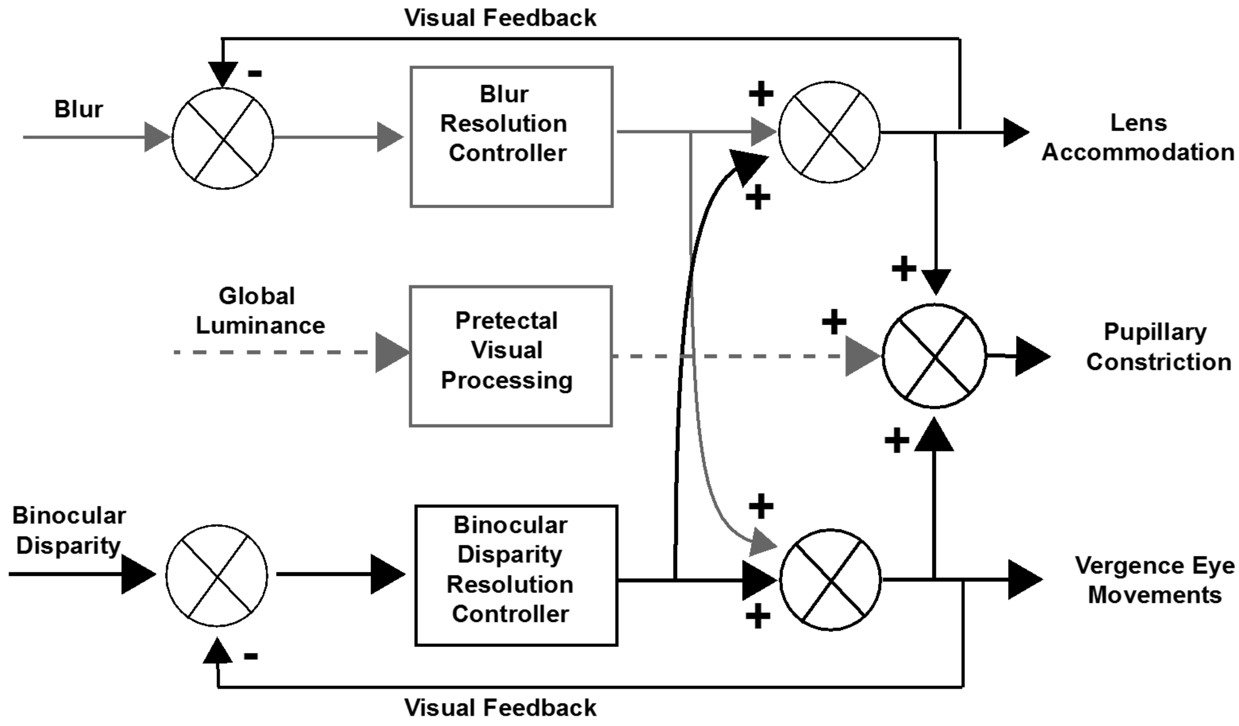
- Convergence insufficiency, determined by static measures of vergence function, has been associated with mTBI

  - Receded near point of convergence amplitude
  - Decreased compensatory fusional ranges at near distances
  - Abnormal phoria at near or far displacements (horizontal, vertical)

Vergence Eye Movements in TBI

- Thiagarajan P, Cuiffreda KJ, Ludlam DP. Vergence dysfunction in mild traumatic brain injury (mTBI): a review. Ophthalmic Physiol Opt 2011, 31: 456-468.
- Alvarez TL, Kim ET, Vicci VR, Dhar SK, Biswal BB, Barrett AM. Concurrent visual dysfunctions in convergence insufficiency with traumatic brain injury. Optom Vis Sci 2012, 89:1740-1751
- Tyler CW, Likova LT, Mineff KN, Elsaid AM, Nicholas SC. Consequences of traumatic brain injury for human vergence dynamics. Front Neurol 2015, 5:282

Coordinated Accommodation, Vergence, and Pupil Activity



Study Design

- mTBI subjects and controls were tested at three sites:
  - University of Miami Miller School of Medicine
  - Madigan Army Medical Center
  - Naval Medical Center San Diego

- All mTBI subjects were diagnosed by an emergency room physician

- mTBI subjects tested using the following time line

Control Subjects

- 36 male (69.2%), 16 female (30.8%)
  - Mean: 28.7 years
  - Range: 21 to 45 years
  - SD: 6.3 years

mTBI subjects

- 13 male (76.5%), 4 female (23.5%)
  - Mean: 29.1 years
  - Range: 20 to 43 years
  - SD: 8.1 years

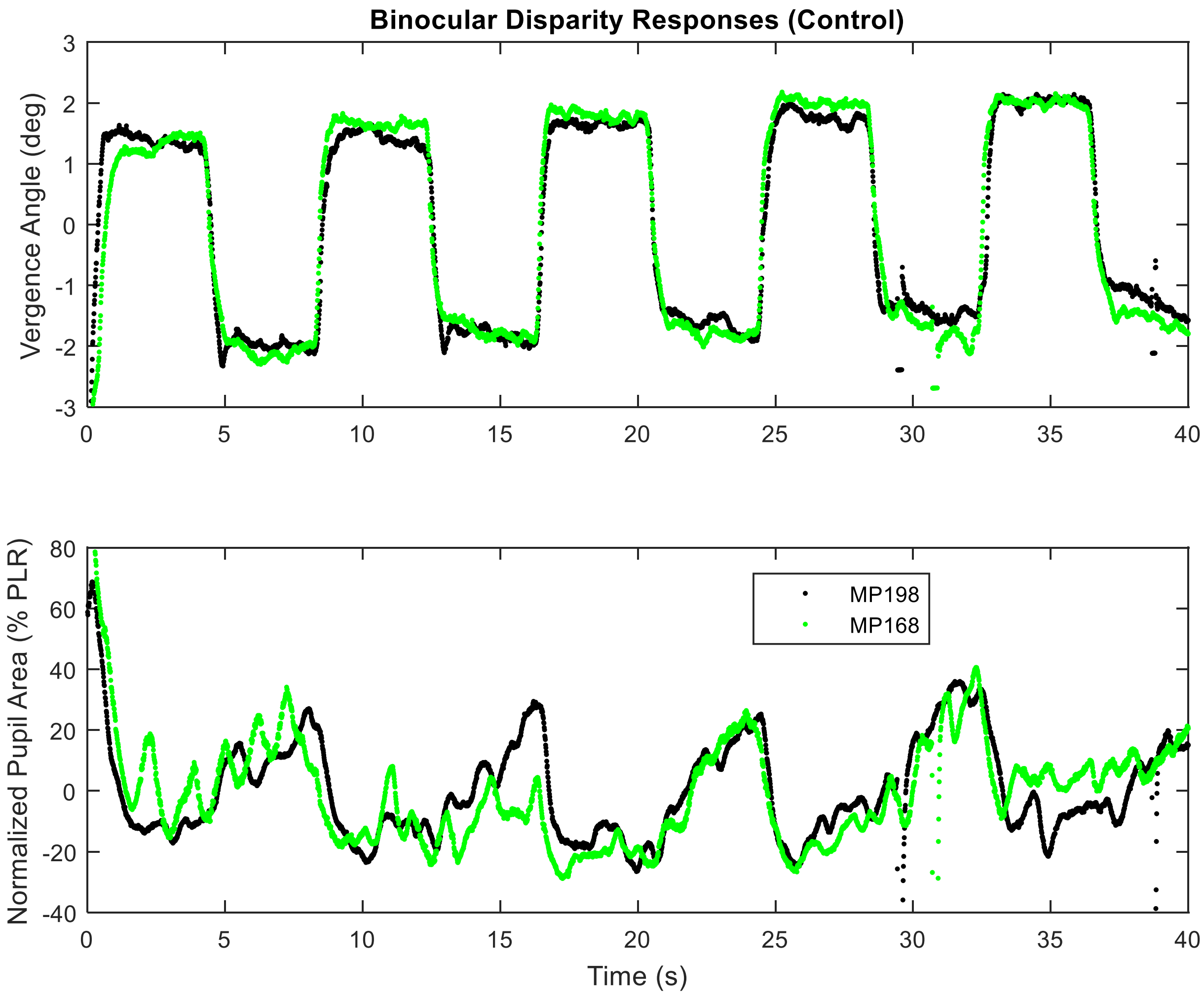
I-PAS Vergence Tasks

- **Each eye viewed a white square with red center (0.1° visual angle)**
  - **Disparity fusion task: Disparity shifts in the horizontal plane equivalent to symmetric, approximately ± 1.4° vergence eye movement steps.**
  - **Disparity pursuit task: Sinusoidal convergence (toward nose) and divergence (laterally) movement in the horizontal plane equivalent to symmetric, approximately ± 2.5° vergence pursuit at 10 sec/cycle.**

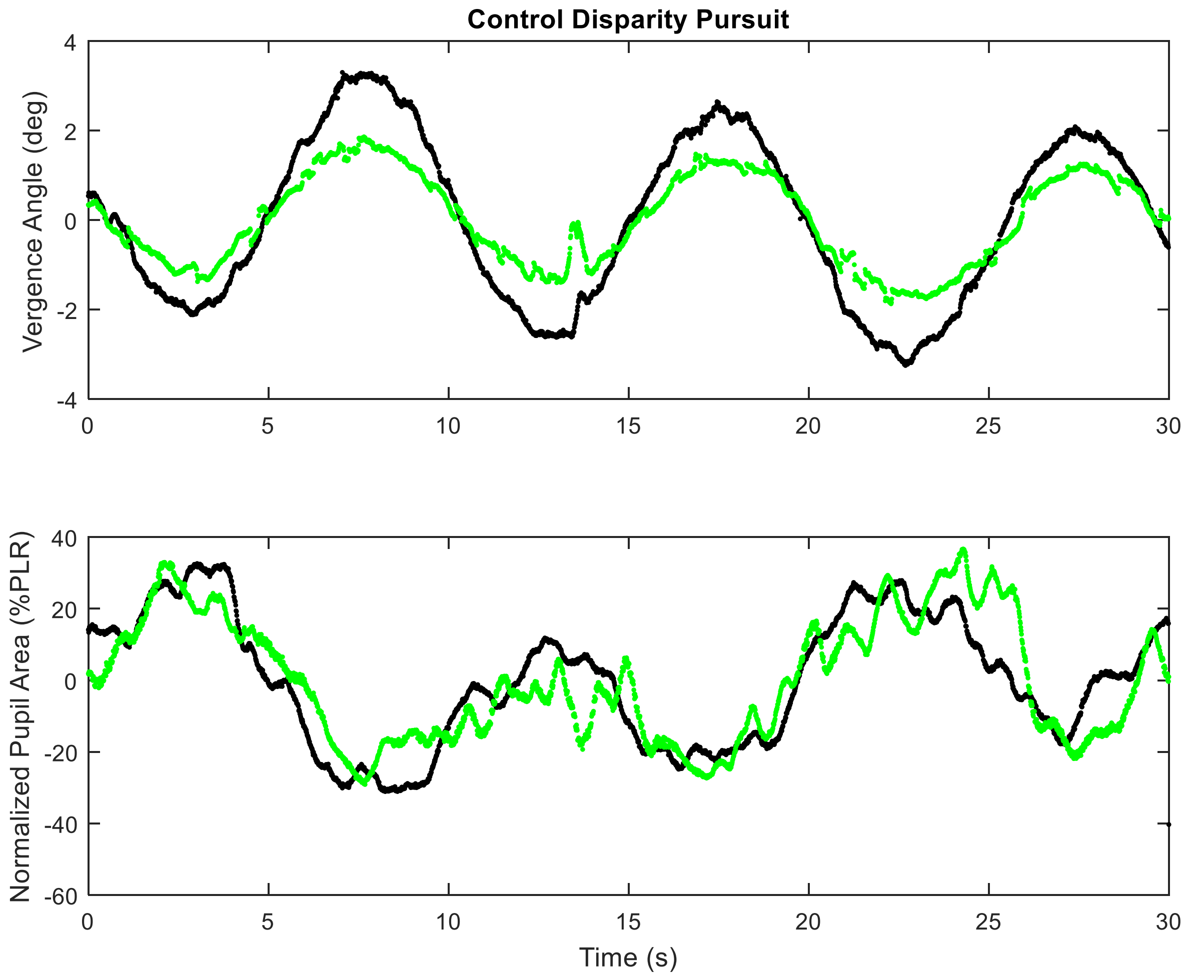
Data Analysis

- Pupillary light response test used to normalize pupil area
  - 0.42 to 65.4 cd/m^2 homogeneous illumination steps
- Vergence angle represented in degrees relative to zero at initial fixation

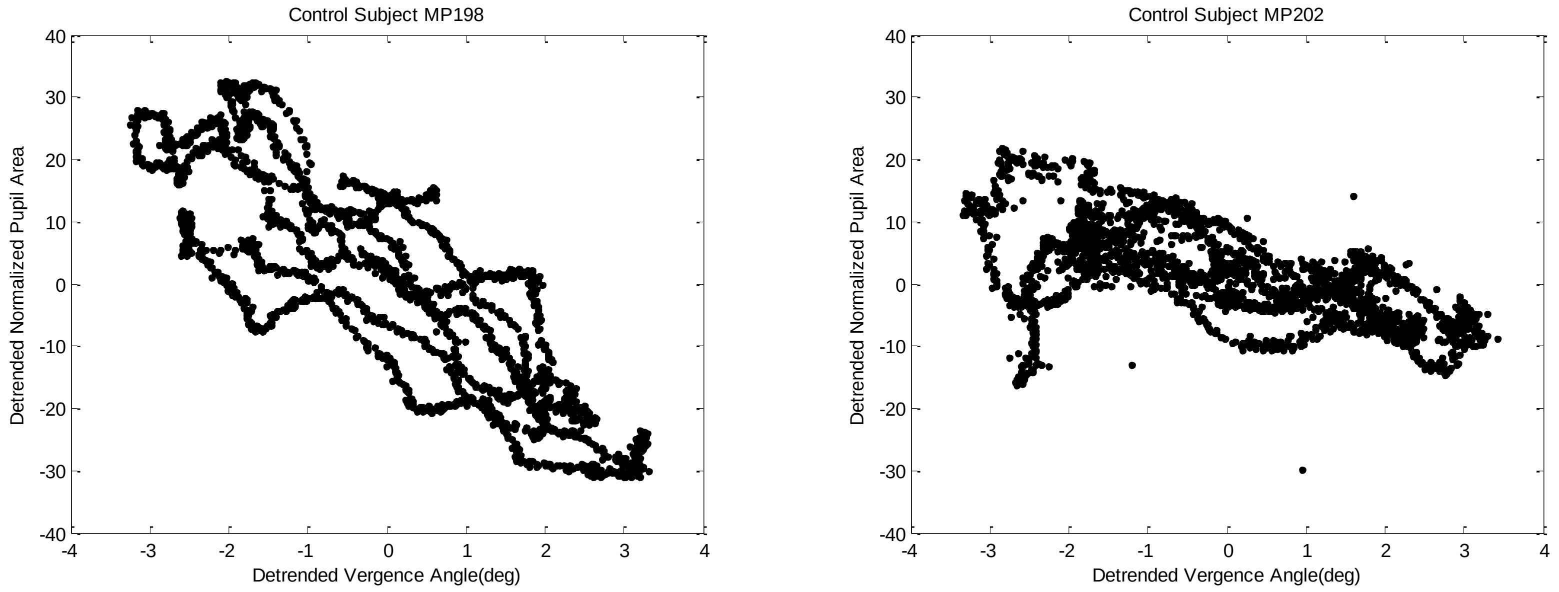
Control Subjects: Disparity Fusion Task



Control Subjects: Disparity Pursuit Task



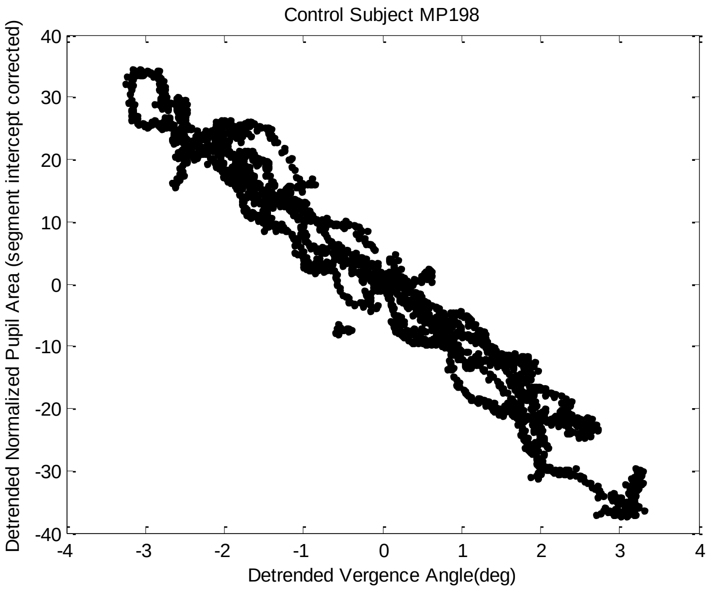
Control Subjects: Variability Examples (Detrended Vergence-Pupil Coordination)

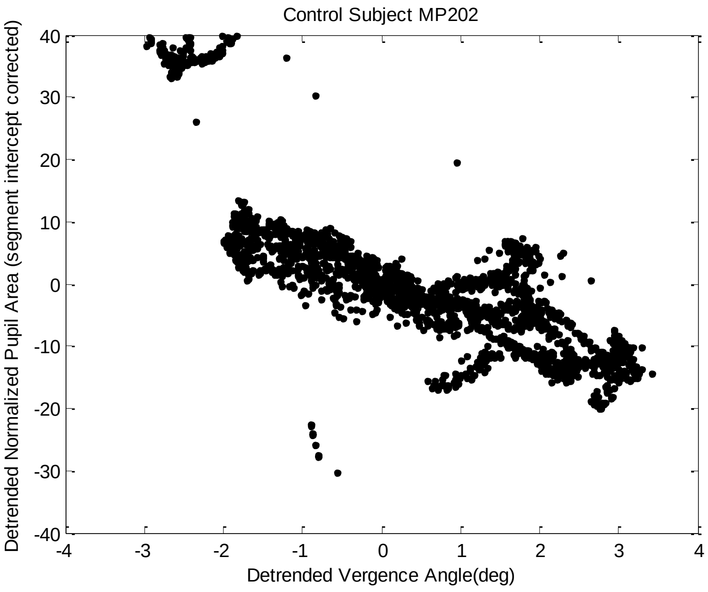


Piecewise Linear Analysis of Eye and Pupil Movement Coordination

- The sampled detrended normalized pupil area and detrended vergence angles are a multivariate time series
- A modified Gath-Geva clustering algorithm (Abonyi et al. Fuzzy Sets and Systems 149:39–56, 2005) was used for objective fuzzy segmentation of the time series into 15 segments with homogeneous properties.
  - Clustering algorithm for simultaneous identification of local probabilistic principal component analysis models
  - Based upon measured homogeneity of the segments and fuzzy sets used to represent the segments in time.
  - One principal component selected (represents the association between eye and pupil movements)

Plots After Subtraction of Linear Segment Intercept

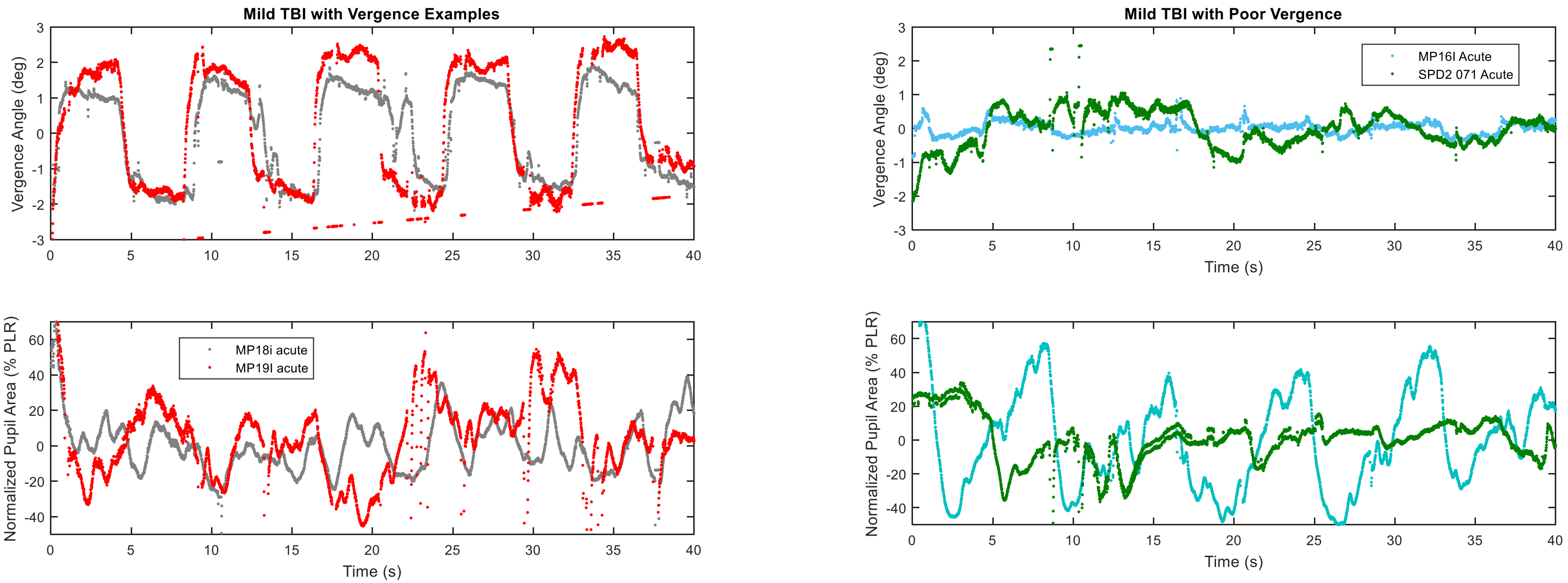




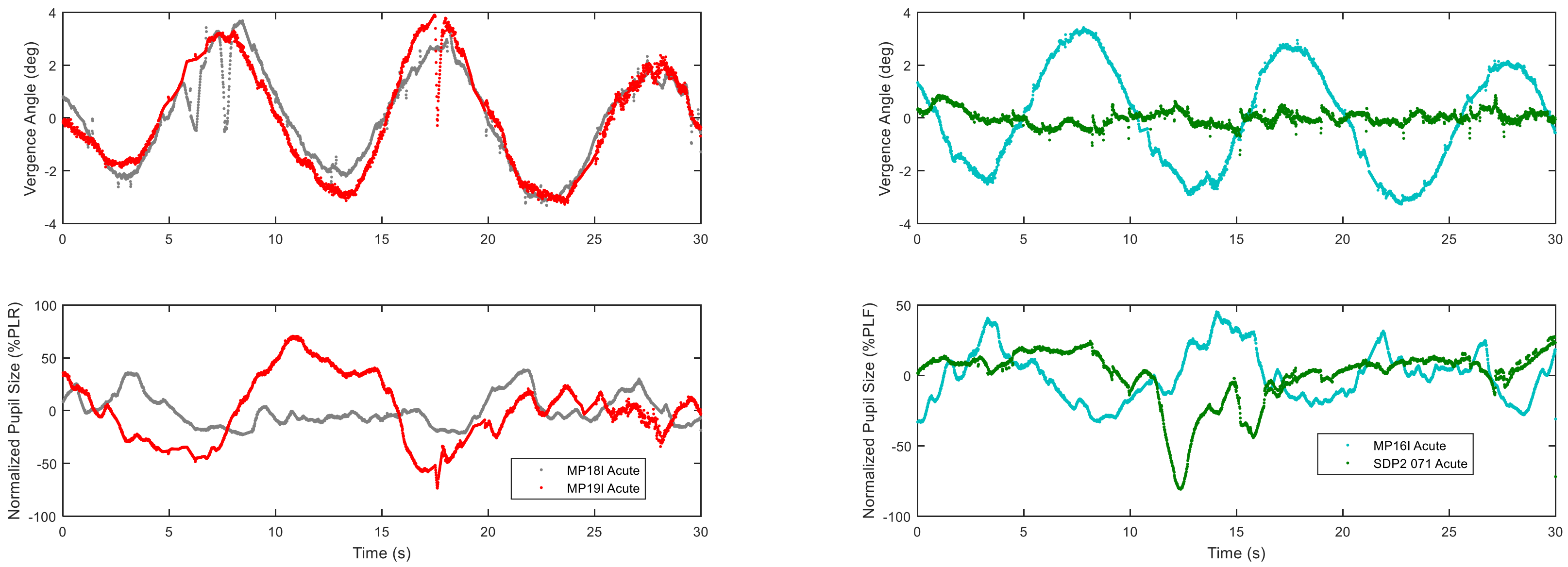
R^2=0.948

R^2=0.663

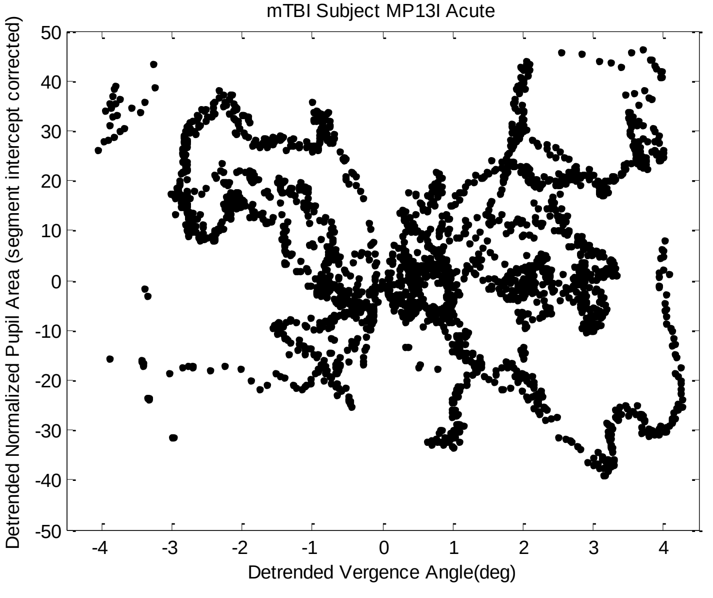
mTBI Subjects: Variability Examples (Detrended Data)

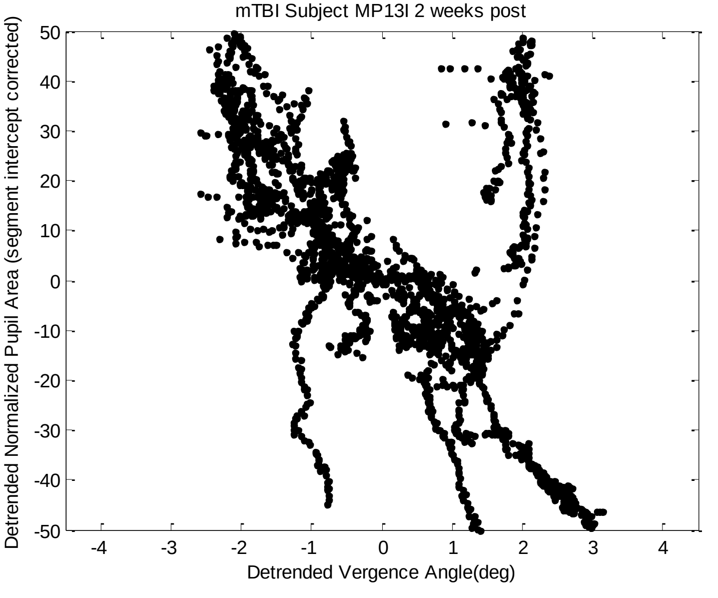


mTBI Subjects: Variability Examples (Detrended Data)



Plots After Subtraction of Linear Segment Intercept: mTBI example





R^2=0.195

R^2= 0.275

Conclusions

- In acute mTBI, a majority of patients showed
  - Depressed modulation magnitude and increased variability for ocular convergence (smooth pursuit)
  - Depressed modulation magnitude and increased variability of pupil constriction during convergence
  - Diminished coordination between the ocular convergence and pupil responses
- The performance recovered within 2 weeks in this small cohort of 17 mTBI subjects

Prospects for Operational Monitoring of Eye and Pupil Movements

- Detecting effects of directed energy exposures in the field
- Pupil responses are sensitive to oxygenation status and altitude
  - Undersea hypoxia or hypercarbia
  - OBOG issues (include noise exposures)
- Unobtrusive interfaces with virtual and augmented reality platforms